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SECURITY CLASSIFICATION OF THIS PAGE

AD-A195 216 MENTATION PAGE

Form Approved
OMB No 0704-0188
Exp Date Jun 30 1986

1a R	1b RESTRICTIVE MARKINGS
2a SECURITY CLASSIFICATION AUTHORITY UNCLASSIFIED	3 DISTRIBUTION / AVAILABILITY OF REPORT
2b DECLASSIFICATION / DOWNGRADING SCHEDULE UNCLASSIFIED	
4 PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a NAME OF PERFORMING ORGANIZATION Dpt. of Bact Dis, CD & I 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION WRAIR
6c. ADDRESS (City, State, and ZIP Code) Washington, DC 20307-5100	7b. ADDRESS (City, State, and ZIP Code) Washington, DC 20307-5100
8a. NAME OF FUNDING / SPONSORING ORGANIZATION Ft. Detrick, Frederick, MD 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) USAMRDC Ft. Detrick, Frederick, MD 21702-5012	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. / PROJECT NO. / TASK NO. / WORK UNIT ACCESSION NO.

11. TITLE (Include Security Classification)
PATHOGENESIS AND MANAGEMENT OF GONORRHEA

12. PERSONAL AUTHOR(S)
TRAMONT, E.C., BOSLEGO JW

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
MANUSCRIPT	FROM _____ TO _____		

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

DTIC ELECTE JUL 0 8 1988 S D

20 DISTRIBUTION / AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	21 ABSTRACT SECURITY CLASSIFICATION
22a. NAME OF RESPONSIBLE INDIVIDUAL Edmund C. Tramont	22b TELEPHONE (Include Area Code) / 22c OFFICE SYMBOL

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted
All other editions are obsolete

SECURITY CLASSIFICATION OF THIS PAGE

UNCLASSIFIED

From: UROGENTIAL INFECTIONS
Edited by Amedeo Bondi, Donald D. Stieritz,
Joseph M. Campos, and Linda Ann Miller
(Plenum Publishing Corporation, 1987)

PATHOGENESIS AND MANAGEMENT OF GONORRHEA

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Gonorrhea is one of the oldest recorded diseases of mankind (1). Over the past 15 years it has reached epidemic proportions, afflicting principally the most sexually active 15-30 years old age group at a rate of 12/1000/yr. The reasons for such high rates are multifactorial. Increased promiscuity among sexually active adults, the propensity of gonorrhea to remain asymptomatic, the unique epidemiology of the disease and increased antibiotic resistance have all played important roles.

Gonorrhea rates have always been particularly high in the Armed Forces, (2) and presently remain 6 times that of a matched U.S. civilian cohort.

ANTIBIOTIC RESISTANCE

Chromosomally mediated resistance to penicillin has steadily progressed since 1945. Three separate mutations designated Pen A, Pen B, and mtr which are additive have been documented (3,4). The net effect has been that an increasing proportion of strains have become resistant to 2 mcg/ml of penicillin, the in vitro correlate of treatment failure (4). Indeed, the steady increase in resistant strains isolated from the Far East (where historically resistance patterns have changed before those in the U.S.) was documented in 1974 (5). By 1983, treatment failure outbreaks traced to chromosomally mediated resistance had been reported in North Carolina, Tennessee, New Mexico, and Oregon (6). These mutations increase the resistance to penicillin by decreasing the affinity of penicillin binding proteins for beta-lactam antibiotics, by decreasing the permeability of the gonococcal outer membrane, and/or by altering the concentration of penicillin binding proteins (4,7,8).

The first treatment failure due to penicillinase producing N. gonorrhoeae (PPNG) was recorded in 1976 and traced to a contact in the Far East. By 1982, the incidence of PPNG strains in the Far East had skyrocketed to 46% (9). This dictated a change in the treatment-of-choice

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regimen from penicillin to spectinomycin. However, a steady increase in spectinomycin resistant strains has already been reported (9).

Fortunately, a number of newer antibiotics have proved effective for both PPNG and spectinomycin resistant strains (10,11,12). Their principal drawback at this time is cost, a particularly troublesome problem in developing countries.

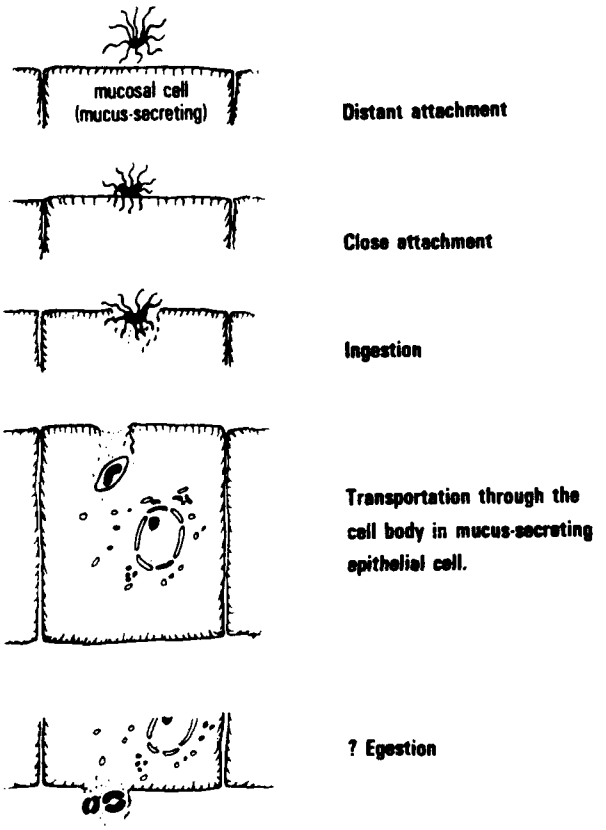

FIGURE 1. THE PATHOGENESIS OF GONOCOCCAL INFECTION

MOLECULAR BIOLOGY

Much has been learned in recent years about the molecular biology of N. gonorrhoeae. The steps in pathogenesis can be broken into 5 stages (1) distant attachment, (2) close attachment (3) ingestion by mucus-secreting cells (4) transportation through the cell body in phagosomes and (5) egestion through the basement membrane (Fig. 1).

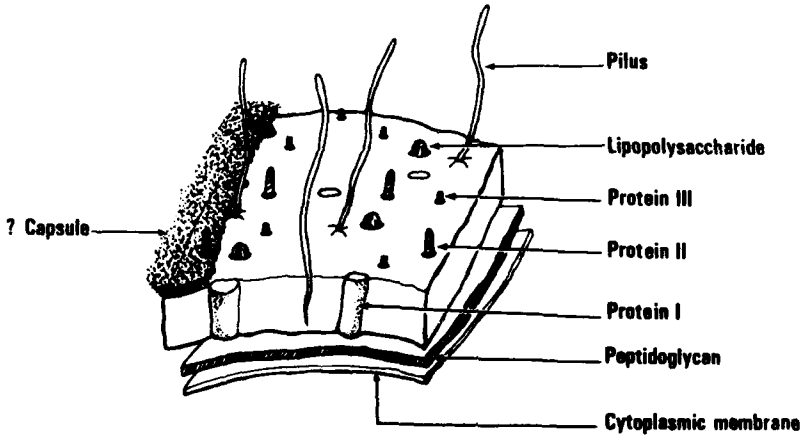

FIGURE 2. SCHEMATIC DIAGRAM OF GONOCOCCAL CELL WALL ADAPTED FROM WHO/VDT/RES/CON/82.137

PILI

N. gonorrhoeae pili (Fig. 2) are protein organelles of attachment to eukaryotic cells (13,14,15) and they are principally responsible for distant attachment. Antigenically, they consist of a common portion which is shared among all gonococcal pili and a distinct variable portion unique to each strain (16,17,18,19), a situation analogous to the antigenic nature of immunoglobulins. Pili also increase resistance to phagocytosis. A meaningful pilus typing system has not yet been developed.

PROTEIN I

Protein I functions as a porin, which is a transmembrane channel that permits the exchange of hydrophilic molecules through the hydrophobic outer membrane and is responsible for directly transferring the gonococcus into eukaryotic membranes (20). It has been suggested that they are responsible for increased resistance of gonococci to the lytic activity of normal human sera (21). There are 10-20 known Protein I types.

PROTEIN II

Protein II is also referred to as the opacity protein because it imparts an opaque quality to colonies grown on modified culture media (22). Opaque colonies tend to be isolated from the male urethra and during the mid-cycle of the menstrual period. Transparent colony types are associated with other phases of the menstrual cycle, fallopian tube and blood isolates. Opaque (O) and transparent (Tr) colony types may or may not be piliated.

PROTEIN III

All gonococcal strains have a single protein known as Protein III. It is closely associated to Protein I, but its specific role or function is not yet known (20).

LIPOPOLYSACCHARIDE

Gonococcal lipopolysaccharide has been associated with susceptibility to bacteriocidal antibody (23) and cytotoxic activity for ciliated cells of the human fallopian tube (24).

CAPSULES

A gonococcal capsule has been described but never isolated (25,26). It has been associated with resistance to phagocytosis (25).

IgA PROTEASE

Gonococci elaborate an IgA protease which cleaves IgA immunoglobulin at the hinge region (27). The role of IgA protease in infection has not yet been clearly defined.

IRON BINDING COMPOUNDS

Like most mucosal pathogens, gonococci are efficient scavengers of iron (28). There is evidence that blood and joint isolates, Disseminated Gonococcal Infection (DGI) strains, are more efficient than non-DGI strains (29).

IMMUNOLOGY

A variety of serological tests that have been developed over the years have repeatedly demonstrated the following: (1) a humoral antibody immunologic response can be invoked by a gonococcal infection, (2) the magnitude and characteristics of the response are not predictable but tend to be more brisk in women, (3) the cross-reactivity with antibody induced by other organisms (natural antibody) is significant and, (4) neither the type or level of antibody correlates with protection.

Local secretory antibody has also been described (30). This antibody functions primarily by blocking the attachment of gonococci to epithelial eukaryotic cells, and this functional aspect of local antibody is directed principally at pili (31). This antibody is broadly cross-reactive against heterologous strains (30-32).

Repeated gonococcal infections are common suggesting that immunity does not exist. However, Mahoney, et al. (33) demonstrated relative resistance to infection which correlated with a history of previous gonococcal infections (older prostitutes have fewer episodes of symptomatic gonorrhea), and Brinto, et al. have demonstrated significant protection in a human challenge model (34).

Nevertheless, there are many factors which appear to mediate against effective immunity to gonorrhea. Immunity may be strain specific and the heterogenicity of pili and cell membrane Protein I or Protein II may thus mediate against the development of broad resistance. Immunity may be easily overwhelmed. Local antibody, which principally acts by directly blocking the attachment of gonococci to mucosal cells, lacks the augmentation and efficiency supplemented by complement (bacteriocidal or opsonic antibodies). Thus, a small number of organisms can overwhelm the host's immune status. Indeed, Brinton, et al. found that increasing the concentration of organisms from 10^3 to 10^5 organisms increased infectivity from $\leq$10% to $\geq$90% in a human challenge model (34).

CLINICAL SYNDROMES

Urethritis and Cervicitis. Urethritis and cervicitis are the most common clinical presentations of gonorrhea. In contrast to long held views, gonococcal cervicitis is symptomatic in about 50% of cases. The reasons for this misconception stems from the earlier descriptions of patients referred to sexually transmitted disease clinics as contacts, the failure to culture urine of high risk patients on appropriate culture media and the nonspecific nature of the complaints. The complaints, which range from lower abdomen pain, urgency, frequency and vaginal discharge, are most prominent at the time of menses and are often disregarded as dysmenorrhea.

Pelvic Inflammatory Disease (PID). Women bear a disproportionate amount of the morbidity due to sexually transmitted disease. The incidence of PID and ectopic pregnancy is increasing. At least 40% of cases of PID are due to gonorrhea. Once PID occurs, the individual is at greater risk of suffering a second episode. Infertility increases with each episode (35), and by the time the patient has suffered her sixth episode of PID, she has a 95% chance of being sterile.

A strategy to protect against the development of PID with a Protein I vaccine has been proposed and is undergoing phase I trials (Buchanan, T., personal communication).

Epididymitis. Epididymitis is the male equivalent of PID. Today, chlamydia causes epididymitis among young sexually active men more often then N. gonorrhoeae (36).

Asymptomatic Carriage. Asymptomatic carriage occurs most often in women, although 10-15% of men are also asymptomatic. However, a careful history will often elicit the presence of a slight discharge ("do you stain your underwear?"), abdominal discomfort or urinary tract symptoms.

Oropharyngitis. Approximately 5% of all individuals who report to a STD clinic with gonorrhea have gonococcal pharyngitis manifested by a severe sore throat. Oral-genital sex is the most frequent antecedent history. The clinical microbiology laboratory must be advised to plant the throat specimen on selective media. A Gram stain revealing intracellular Gram negative diplococci is very suggestive (in the appropriate setting). Oropharyngitis is an important consideration affecting antibiotic treatment (see below).

Conjunctivitis. Gonococcal conjunctivitis may be a consequence whenever a fetus passes through an infected or colonized birth canal. The incidence of neonatal conjunctivitis decreased significantly after the institution of silver nitrate eye drops. Adults may also develop conjunctivitis. (N. gonorrhoeae, like most genital tract pathogens, have a tropism for the conjunctiva and the oropharynx).

Proctitis. Gonococcal proctitis, a potential consequence of anal sex, often presents with a discharge, tenesmus or rectal abcess.

Disseminated Gonococcal Infection (DGI). DGI occurs most often in women, especially during menses and late pregnancy. It has been speculated that these strains have an increased capacity to utilize free iron, and therefore behave in a more virulent fashion (29). DGI strains in this country tend to be of an A⁻H⁻U⁻ auxotype, quite sensitive to penicillin (37,38) and resistant to the lytic activity of normal serum (39,40).

Tenosynovitis and septic arthritis are the most common complications of DGI. Endocarditis and meningitis are quite rare. Most patients present with fever and migratory synovitis which finally "settles" in one joint. The knee and elbow are the most frequently involved joints. Skin lesions, which range from tiny macula to discrete pustules, characteristically develop on the ankles, feet, wrist, hands and fingers.

DIAGNOSIS

The Gram stain and culture remain the most reliable methods to diagnose gonorrhea. The Gram stain is 93-99% specific for gonococcal urethritis or cervicitis. It is 93% sensitive in men but only 60% sensitive in women. Therefore, one should always perform a Gram stain on specimens obtained from both sexes, but a negative Gram stain in a women requires a culture before assigning an alternative diagnosis.

Culture on selective media remains the most sensitive means of diagnosis in women. As noted above, urine cultures on selective media for N. gonorrhoeae are under used! (N. gonorrhoeae is an important etiologic agent causing the urethral frequency syndrome and urine cultures on selective media for N. gonorrhoeae should be done on all sexually active populations.)

A number of newer techniques utilizing monoclonal antibodies and DNA hybridization have recently been introduced. To date, they are not superior to the Gram stain or culture, but offer hope for a quicker diagnosis in women by eliminating the 24-48 hr delay for culture results.

TREATMENT

Penicillin remains the treatment of choice for uncomplicated gonorrhea in the United States (1984) (Table 1) (4). How long this will

TABLE 1. Treatment of Uncomplicated Gonorrhea

Aqueous procaine penicillin G (APPG), 4.8 m units IM plus 1.0 gm Probenicid PO [1,2]
or
Amoxicillin, 3.0 gm plus 1.0 gm Probenicid PO[1]
or
Ampicillin, 3.5 gm plus 1.0 gm Probenicid PO[1]
or
Spectinomycin, 2.0 gm IM[1]

[1]Plus doxycycline 100 mg PO bid or tetracycline 500 mg PO qid X 7 days.
[2]Recommended for homosexual men and pharyngeal infections.

remain the case is conjecture. Penicillin cannot be used in patients who have contracted their illness in the Far East. Spectinomycin is the drug of choice for patients infected with PPNG strains but the rapid increase in spectinomycin resistance is troublesome. Ampicillin 3.5 gm or Amoxicillin 3.0 gm given orally with 1 gm of probenecid can be substituted for penicillin. Because at least 40% of patients have a concomitant chlamydia infection, the addition of a tetracycline antibiotic is important, especially when the ability to verify the diagnosis of chlamydia is poor or lacking. Doxycycline 100 mg bid or tetracylcine 0.5 gm qid for 7 days is usually adequate (42).

Patients with DGI should be hospitalized to rule out endocarditis, meningitis, and optimally manage septic joints. Since patients with disseminated gonococcal infection are usually infected with strains that are quite sensitive to penicillin, hospitalization for 3 days of intravenous penicillin is usually adequate to cure the infection (37). Furthermore, surgical drainage of infected joints is not necessary.

Patients with gonococcal oropharyngitis are more difficult to treat, and may require more then one course of treatment. Spectinomycin is not reliable as treatment for pharyngeal gonorrhea (43).

Since pelvic inflammatory disease is so frequently a mixed infection and the possible consequence is so devastating, antimicrobial combinations to cover N. gonorrhoeae, anaerobic bacteria, enterobacteriaceae and C. trachomatis are warranted (Table 2). PPNG strains may be treated with a variety of newer antibiotics (Table 3).

TABLE 2. Treatment of Pelvic Inflammatory Disease

		Daily Dose
Anaerobic Coverage		
Cefoxitin	IM or IV	2.0-8.0 gm
Metronidazole	PO or IM or IV	1.0-2.0 gm
Enterobacteriaceae		
Cefoxitin	IM or IV[2]	2.0-8.0 gm
3rd generation cephalosporin[2]	IM or IV	
Aminoglycoside	IM or IV[2]	
Chlamydia		
Doxycycline	PO or IV[3]	100-200 mg

[1]The length of treatment depends upon severity of disease. Most often 10-14 days of treatment is sufficient. Toxic patients should be admitted to the hospital.
[2]Daily dose depends on drug chosen and renal status.
[3]14 days of treatment.

TABLE 3. Treatment PPNG (Anywhere where incidence is greater than 1%)

Spectinomycin, 2.0 gm. IM
or
Cefoxitin, 2.0 gm. IM
or
Cefotaxime, 1.0 gm. IM plus 1.0 gm probenicid PO
or
Ceftriaxone, 250 mg. IM
or
Norfloxacin, 1200 mg. PO

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